THREO-DOPS CONTROLLED RELEASE FORMULATION

DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical formulations for the controlled delivery of threo-3-(3, 4-dihydroxyphenyl)serine (threo-DOPS), and derivatives thereof. Threo-DOPS exists as the optically active L- and D-forms and the racemic DL form. The L-threo-DOPS is preferred for the purposes of this invention. Such formulations can contain an extended or slow release component that maintains therapeutic concentration of threo-DOPS in the blood plasma over a prolonged time period. They can be further combined with an immediate release formulation to produce a product that, when administered to a patient in need thereof, results in a rapid attainment of a therapeutic effect, followed by substantially steady levels of active drug, eliminating the sharp peaks and troughs in blood plasma drug levels experienced with the existing threo-DOPS formulations. These formulation are especially useful in the treatment of conditions associated with norepinephrine (NE) dysfunction, and which benefit from the controlled release of threo-3-(3, 4-dihydroxyphenyl)serine compounds, such as the pain associated with migraines, and disorders associated with sympathetic nervous system dysfunction such as orthostatic hypotension, orthostatic intolerance, etc.

A pharmaceutical formulation of the present invention includes a controlled release pharmaceutical formulation, comprising: an effective amount of threo-3-(3, 4-dihydroxyphenyl)serine, a derivative thereof, or a pharmaceutically-acceptable salt thereof, in an extended release form. A controlled release formulation can be effective for any desired period of time, e.g., oral dosage units can be produced that are effective for once-daily, twice a day (about every 12 hours), or three times (about every 8 hours) a day administration.

The phrase "controlled release" indicates that the release of the active ingredient is regulated or modulated to achieve a desired rate of delivery into the systemic circulation. A controlled release formulation can be pulsed, delayed, extended, slow, steady, immediate, rapid, fast, etc. It can comprise one or more release formulations, e.g. extended- and immediate- release components. For example, to prevent pain, such as the pain associated with migraine headaches, an oral controlled release formulation can

comprise a plurality of components positioned in any suitable arrangement, e.g., comprising a "free" drug in a rapidly soluble polymer film on the outside of the dosage unit to achieve an immediate therapeutic effect, and an extended release delivery system in the core of the unit to produce steady state concentrations of drug to prevent recurrence of the pain. A formulation can be a composition of matter, a device, a patch, multi-layered or multi-configured products, etc.

The terms "extended release", "immediate release", etc., have their conventional meanings. An extended release composition is one in which the active ingredient is not released immediately in its active form, but is slowly and controllably discharged from the dosage unit. The kinetics of the extended release are influenced by the choice of the delivery system, amount of the active ingredient, dissolution rate of the drug, compartment in which release occurs (e.g., with oral delivery systems, this is the gastrointestinal tract), absorption of drug from the site of release into the systemic circulation, drug distribution from the systemic circulation, etc. An immediate release formulation can be used to deliver the equivalent of a "bolus" to the body, releasing the active form of the drug directly into the targeted physiological compartment (e.g. the GI tract) to achieve rapid systemic availability.

Any suitable extended release delivery system can be used in accordance with the present invention to achieve the slow release of threo-DOPS. Several are discussed below, but any effective system can be used without limitation.

1. Dissolution controlled release. Drug particles or granules that have a reasonable aqueous solubility, such as threo-DOPS, can be coated with, or embedded in, a slowly soluble material. The coated particles or granules can subsequently be compressed into tablets or filled into hard gelatin capsules. Drug can also be applied to the surface of non-pareil seeds, which can then be coated and formulated into either tablets or capsules.

Coating materials include, but are not limited to, shellacs, beeswax, glyceryl monostearate, glyceryl palmostearate, stearyl alcohol, ethylcellulose, cellulose acetate phthalate, acrylic resins, methacrylate hydrogels, methylmethacrylate, polymethacrylate, polylactic acid, polyvinyl chloride, polyvinyl chloride, polymethacrylate,

hydroxypropylmethylcellulose, polyethylene glycols, carboxymethylcellulose, sodium carboxymethylcellulose, etc.

2. Diffusion controlled release. Two main types of diffusion controlled systems are typically used: reservoir devices and matrix devices. In a reservoir device, a water-insoluble polymeric material surrounds a drug-containing core, which can be a tablet, or particles or granules that are subsequently formulated into a tablet or a capsule. Materials used as coatings in reservoir devices include hydroxypropylcellulose/polyvinyl acetate combinations, polyethylene glycol/ethylcellulose combinations, ethylcellulose, and poly (hydroxymethacrylate).

With matrix devices, the drug is dispersed in an insoluble matrix consisting of such materials as hydrated methylcellulose, carnauba wax and stearyl alcohol combinations, carbopol, glyceryl tristearate, methyl acrylate/methyl methacrylate combinations, and polyvinyl chloride and polyethylene, alone and in combination.

3. Diffusion and dissolution controlled release. In this delivery system, the drug core is encased by a partially-soluble membrane. Dissolution of the soluble portion of the membrane facilitates diffusion of drug through the resultant pores of the polymer coat. An example of this type of coating system is ethylcellulose/methylcellulose combinations.

4. Ion-exchange resins. This approach is based on the presence of ions in the gastrointestinal tract which will exchange with the drug ions present in the resin. The drug-charged resin is prepared by mixing the resin with a solution of the drug, followed by washing and then drying to form particles or beads. These are then filled into gelatin capsules or suspended in an appropriate vehicle; prior to this step, they may be film-coated using one or more of the agents listed in sections 1 and 2 above. In one such system, drug-containing resin particles are coated with polyethylene 4000 and then with ethylcellulose.

5. pH-independent release. The addition of buffers to the drug delivery system can be utilized in such a concentration so as to cause the drug to be released at a rate that is independent on the pH in the gastrointestinal tract.

6. Osmotically controlled release. In this type of delivery system, a core containing the drug and an appropriate amount of an osmotically active salt is surrounded

by a semipermeable membrane that is both rigid and non-swelling. The membrane is permeable to gastrointestinal fluid but impermeable to the drug in solution. Following administration, gastrointestinal fluids diffuse across the semipermeable membrane, thereby dissolving the drug and osmotically active salt to set up an osmotic pressure within the delivery system. Drug solution is then pushed through a laser-drilled orifice in to the gastrointestinal tract at a constant (zero order) rate until all of the osmotically active salt is depleted.

7. Altered density formulations. This approach relies on the formation of a low density, buoyant, drug-containing tablet matrix. As a result, the delivery system tends to remain floating on top of the stomach contents, dispensing drug in a uniform manner.

In an immediate release component, the release kinetics are largely dependent on the solubility of threo-DOPS. The active drug can be mixed with any conventional soluble excipient (such as lactose), or formulated with a soluble polymer that readily and directly dissolves in the targeted compartment (e.g., GI tract). The threo-DOPS can also be modified to improve its solubility, e.g., by physical (micronized to reduce particle size) treatment, the use of permeation enhancers, or chemical treatment.

Threo-3-(3,4-dihydroxyphenyl)serine (also known as threo-DOPS or droxidopa) is a synthetic amino acid precursor of NE (Freeman R., *Clin. Neuropharm.*, 14, 296-304, 1991). It has four stereoisomers, L-threo-DOPS, D-threo-DOPS, L-erythro-DOPS, and D-erythro-DOPS. Of the four, L-threo-DOPS is preferred, but a racemate can also be used. L-threo-DOPS is directly converted to NE via the actions of dopa decarboxylase (DDC) (also known as L-aromatic amino acid decarboxylase or AAAD). Peak plasma levels of L-threo-DOPS occur 3 hour after oral ingestion whereas peak NE levels occur 5 hours after ingestion. Increased plasma levels of both molecules remain at least 12 hours after oral administration of L-threo-DOPS (S Suzuki T, Higa S, Sakoda S, Ueji M, Hayashi A, Takaba Y, Nakajima A.; Eur J Clin Pharmacol 1982;23(5):463-8). Specific uptake of threo-DOPS has also been demonstrated in microvessel preparations (Hardebo JE, Falck B, Owman C.Acta Physiol Scand 1979 Oct;107(2):161-7).

Any effective amount of threo-3-(3,4-dihydroxyphenyl)serine can used, e.g., from about 10 mg to about 1000 mg per day, about 50 mg to about 700 mg per day, about 100 to about 500 mg per day, about 100 to about 300 mg per day, etc. An effective amount is

a quantity of threo-DOPS that is useful for achieving the desired therapeutic effect, e.g., preventing pain, maintaining blood pressure, preventing the reoccurrence of a norepinephrine dysfunctional disorder. Effective amounts can be determined routinely, and may vary depending upon the age, health, gender, and weight of a patient, as well as the severity, frequency, and duration of the pain. The choice of the delivery system will also guide the selection of the amounts used. Amounts can be administered in a multiple doses over the course of the day, e.g., in order to achieve a prophylactic effect, or a single dose in a hybrid extended/immediate release form.

Any suitable dosing interval can be used in accordance with the present invention. Extended delivery systems can be utilized to achieve a dosing interval, when orally administered, of once every 24 hours, once every 12 hours, etc. The dosage form/delivery system can be a tablet or a capsule suited for extended release, but a sustained release liquid or suspension can also be used. A controlled release pharmaceutical formulation can be produced which maintains the release of, and or peak blood plasma levels of, threo-3-(3, 4-dihydroxyphenyl)serine, derivative thereof, or salt thereof, over a period of at least 8, 12, 16, 18, 20, 24 hours, etc. With this type of formulation, the threo-DOPS can be continuously released in such a way that it is available and effective for maintaining the nerve terminal pools of norepinephrine.

A dissolution controlled release delivery system can be utilized in accordance with the present invention to provide a controlled release pharmaceutical composition. This delivery system can typically contain one or more of the following constituents: 1) active drug; 2) slowly soluble coating/matrix material (see above, for examples); 3) granulating agent; 4) lubricant (e.g., magnesium stearate); 5) channeling agent (e.g., silicon dioxide); 6) surfactant (e.g., sodium lauryl sulfate, sodium taurocholate or a polysorbate); and 7) filler (e.g., lactose).

An extended release matrix can comprise any amount of matrix material that is necessary to delay the release of threo-DOPS into the systemic circulation, e.g., amounts can be as low as 5-100% of active drug, but can also be 2-, 3-, 5-, 10-fold more than active drug, depending upon the matrix material and the desired delivery kinetics. The active ingredient can be embedded in a matrix that retards dissolution, or the active

ingredient can be coated with a material that has an effect on dissolution, or a combination of both.

As mentioned earlier, an immediate release component can be associated with the extended release component to form a multi-layered or combination system having properties of both. This type of controlled release system can provide an immediate bolus to facilitate the filling of the depleted nerve terminals with norepinephrine, and then a slow release component to maintain threo-DOPS in the circulating blood at levels effective to conserve nerve terminal norepinephrine pools and/or to prevent sympathetic nervous system dysfunction.

A controlled release formulation of threo-DOPS can comprise a quantity of an immediate release preparation of threo-DOPS (or derivatives thereof, or pharmaceutically active salts thereof) combined with a quantity of an extended (slow or delayed) release threo-DOPS (or derivatives thereof, or pharmaceutically active salts thereof). The immediate release component can obtain a maximal release of threo-DOPS within approximately 1-3 hours after administration, and then fall toward baseline levels. The extended release component can show a maximal release of threo-DOPS between approximately 6-24 hours after administration. The extended release component can contain multiple and different extended release formulations to broaden the time over which the threo-DOPS is available in active form in the blood stream, e.g., having extended components that have maximal release at 6 hours, 12 hours, and 18 hours, respectively. This can be accomplished by creating multi-layered or multi-component dosage units, where each layer or component displays different dissolution kinetics, or by mixing different immediate and extended release components in a single capsule or tablet. Extended delivery systems can also be utilized that release active drug at roughly the same rate (e.g., zero-order kinetics) for the predetermined delivery period (6, 12, 18, 24 hours, etc.), e.g., using an osmotic delivery system. Effective amounts incorporated into each of the components can be determined routinely. For example, based on the total weight of threo-DOPS (active drug) in the dosage unit, from about 15-55% can be in the immediate release form and from about 45-85% can be in the extended and slow release form, e.g., about 35% in immediate form and 65% in extended release form

Threo-3-(3,4-dihydroxyphenyl)serine can be prepared according to any suitable method. These processes include those described in, e.g., U.S. Pat. Nos. 4,480,109, 4,562,263 and 5,864,041. It can be used as a racemic or optically active isomer, e.g., L-threo-DOPS.

Pharmaceutically-acceptable salts of threo-3-(3,4-dihydroxyphenyl)serine can also be used, including addition salts, e.g., inorganic acids, such as hydrochloric acid, hydrobromic acid, and sulfuric acid, and organic acids, such as fumaric acid, citric acid, tartaric acid, and succinic acid.

Any pharmacologically active derivative of threo-3-(3,4-dihydroxyphenyl)serine can be used. These include, e.g., N-methyl-3-(3,4-dihydroxyphenyl)serine alkyl esters, such as N-methyl-D,L-threo-3-(3,4-dihydroxyphenyl)serine and N-methyl-L-threo-3-(3,4 dihydroxyphenyl)serine, lower alkyl esters, methyl esters, ethyl esters, n-propyl esters, isopropyl esters, etc., as described in U.S. Pat. No. 5,288,898.

In addition to the substances already mentioned, active agents can be further combined with any other suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in *Remington: The Science and Practice of Pharmacy* (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); *Theory and Practice of Industrial Pharmacy* (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); *Encyclopedia of Pharmaceutical Technology* (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002).

These are generally referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic or prophylactic purposes. These include, but are not limited to, antioxidants, preservatives, dyes, tablet-coating compositions, plasticizers, inert carriers, excipients, polymers, coating materials, osmotic barriers, devices and agents which slow or retard solubility, etc.

The active agent of this invention can be in any suitable form, without limitation. Forms suitable for oral use, include, but are not limited to, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, solutions, syrups and elixirs. Compositions intended for oral use may be

prepared according to any method known to the art for the manufacture of pharmaceutical compositions.

The present invention relates to methods of treating a disease in a subject in need thereof, comprising: administering a controlled release pharmaceutical formulation, comprising an effective amount of threo-3-(3, 4-dihydroxyphenyl)serine, a derivative thereof, or a pharmaceutically-acceptable salt thereof, in an extended release form. The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving, etc., a disorder or disease. Diseases that can be treated in accordance with the present invention included, but are not limited to, with sympathetic nervous system dysfunction, Asthma, Hypersensitivity cough, Allergic Rhinitis/nasal congestion, Anorexia Nervosa, Congestive Heart Failure, Chronic Fatigue Syndrome, Depression, Erectile dysfunction, Essential Tremor, Irritable Bowel Syndrome, Migraine, Obesity, Orthostatic Hypotension, Orthostatic Intolerance, Pain, Premenstrual Syndrome/Premenstrual Dysphoric Disorder, Raynaud's phenomenon, Reflex Sympathetic Dystrophy, Overactive/neurogenic bladder, etc.

The examples below illustrate tablet and capsule extended release formulations comprising threo-DOPS. Tablets can be made conventionally, e.g., as described in Tablet Manufacture, *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, Inc., 2002, Pages 2713- 2732. Various diluents, granulating fluids, glidants, etc, are described therein.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The entire disclosure of all patents and publications cited herein are hereby incorporated by reference in their entirety.

EXAMPLES

1. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and compressed into tablets containing:

L-threo-DOPS	100 to 800 mg
Hydroxypropylmethylcellulose (HPMC)	5 to 45%,
Lactose	5 to 20%
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%
Granulation fluid	q.s.

The drug, polymer, and filler are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets.

2. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and compressed into tablets, onto which is applied additional L-threo-DOPS dispersed in an immediate release polymeric film coat containing:

L-threo-DOPS	25 to 300 mg
Ethylcellulose	0 to 5.0%
Hydroxypropylmethylcellulose	0 to 3.0%
Triethyl citrate	0 to 2.0%
Aqueous ethanol	q.s.

The drug, polymer, and filler are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets. The tablets are then spray coated with a polymer solution containing dispersed L-threo-DOPS, sufficient to deliver the required immediate release dose.

3. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and filled into hard gelatin capsules containing:

L-threo-DOPS	100 to 800 mg

Hydroxypropylmethylcellulose (HPMC)	5 to 45%,
Lactose	5 to 20%
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%
Granulation fluid	q.s.

The drug, polymer, and filler are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and filled into hard gelatin capsules.

4. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and blended with an immediate release formulation containing the following before being filled into hard gelatin capsules:

L-threo-DOPS	25 to 300 mg
Lactose	20 to 40%
Microcrystalline cellulose	5 to 15%
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%
Granulation fluid	q.s.

The drug and fillers are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, and blended with lubricant. An appropriate blend of the extended release formulation and the immediate release formulation are prepared and filled into hard gelatin capsules.

5. An extended release hydrophilic matrix formulation prepared by wet granulation using a fluidized bed granulator and compressed into tablets containing:

L-threo-DOPS	100 to 800 mg
Polyvinyl alcohol	20 to 60%
Sodium chloride	10 to 30%
Lactose	10 to 25%

Granulation fluid (e.g., Hydroxypropylcellulose, HPC, 5% solution)	q.s.
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%

The drug, polymer, and fillers are dry blended, and then granulated in a fluidized bed granulator using sufficient granulation fluid to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets.

6. An extended release hydrophilic matrix formulation prepared by wet granulation using a fluidized bed granulator and compressed into tablets, onto which is applied additional L-threo-DOPS dispersed in an immediate release polymeric film coat containing:

L-threo-DOPS	25 to 300 mg
Ethylcellulose	0 to 5.0%
Hydroxypropylmethylcellulose	0 to 3.0%
Triethyl citrate	0 to 2.0%
Aqueous ethanol	q.s.

The drug, polymer, and fillers are dry blended, and then granulated in a fluidized bed granulator using sufficient granulation fluid to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets. The tablets are then spray coated with a polymer solution containing dispersed L-threo-DOPS, sufficient to deliver the required immediate release dose.

7. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and filled into hard gelatin capsules containing:

L-threo-DOPS	100 to 800 mg
Polyvinyl alcohol	20 to 60%
Sodium chloride	10 to 30%
Lactose	10 to 25%
Granulation fluid (Hydroxypropylcellulose, HPC, 5% solution)	q.s.
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%

The drug, polymer, and fillers are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets.

8. An extended release hydrophilic matrix formulation prepared by wet granulation using a high shear mixer and blended with an immediate release formulation containing the following before being filled into hard gelatin capsules:

L-threo-DOPS	25 to 300 mg
Lactose	20 to 40%
Microcrystalline cellulose	5 to 15%
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%
Granulation fluid	q.s.

The drug and fillers are dry blended in a high shear mixer for 5 minutes, at which time sufficient granulation fluid is added to produce a wet granulation that is subsequently dried, screened, and blended with lubricant. An appropriate blend of the extended release formulation and the immediate release formulation are prepared and filled into hard gelatin capsules.

9. An extended release hydrophilic matrix formulation prepared by wet granulation using a fluidized bed granulator and compressed into tablets containing:

L-threo-DOPS	100 to 800 mg
Hydroxypropylmethylcellulose (HPMC)	10 to 50%
Lactose	10 to 25%
Dibasic calcium phosphate	0 to 50%
Microcrystalline cellulose	0 to 25%
Granulation fluid (Polyvinylpyrrolidone, PVP, 4% solution or Hydroxypropylmethylcellulose, HPMC, 3% solution)	q.s.
Magnesium stearate	0 to 1.5%
Silicon dioxide	0 to 0.5%

The drug, polymer, and fillers are dry blended, and then granulated in a fluidized bed granulator using sufficient granulation fluid to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets.

10. An extended release hydrophilic matrix formulation prepared by wet granulation using a high fluidized bed granulator and compressed into tablets, onto which is applied additional L-threo-DOPS dispersed in an immediate release polymeric film coat containing:

L-threo-DOPS	25 to 300 mg
Ethylcellulose	0 to 5.0%
Hydroxypropylmethylcellulose	0 to 3.0%
Triethyl citrate	0 to 2.0%
Aqueous ethanol	q.s.

The drug, polymer, and fillers are dry blended, and then granulated in a fluidized bed granulator using sufficient granulation fluid to produce a wet granulation that is subsequently dried, screened, blended with lubricant, and compressed to form tablets. The tablets are then spray coated with a polymer solution containing dispersed L-threo-DOPS, sufficient to deliver the required immediate release dose.